MAIL STOP APPEAL BRIEF-PATENTS
Attorney Docket No. 27396U

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

NOTCOVICH et al.		Conf. No.:	3336
Serial No:	10/578,860	Art Unit:	1641
Filed:	June 30, 2006	Examiner:	LAM, Ann Y.

For: **SYSTEM AND METHOD FOR CARRYING OUT MULTIPLE BINDING REACTIONS IN AN ARRAY FORMAT**

APPEAL BRIEF

This Appeal Brief is submitted to the Board of Patent Appeals and Interferences appealing the rejection of claims 29-37, 39 and 41-46 set forth in the final Official Action dated January 6, 2011. A Notice of Appeal was filed on May 6, 2011, making an Appeal Brief due on or before July 6, 2011. Accordingly, this paper is timely filed.

1. Table of Contents

2. The Real Party in Interest

The real party in interest in this appeal is the assignee, BIO-RAD HAIFA LTD., which is a wholly owned subsidiary of BIO-RAD LABORATORIES, INC.

3. Related Appeals and Interferences

Appellants are not aware of any other appeals or interferences that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal.

4. Status of Claims

The status of the claims is as follows upon filing of this Appeal Brief:

Claims pending: 29-37, 39 and 41-46;

Claims cancelled: 1-28, 38 and 40;

Claims withdrawn: N/A;

Claims objected to: 29 and 37;

Claims allowed: N/A; and

Claims rejected: 29-37, 39 and 41-46.

The claims on appeal are claims 29-37, 39 and 41-46.

5. Status of Amendments

Appellants filed a Preliminary Amendment on May 11, 2006, in which claims 1-28 were cancelled and claims 29-46 were added.

On July 7, 2007, responsive to the Official Action dated April 7, 2008, Appellants filed an Amendment and Response in which claims 38 and 40 were cancelled and claims 29-35, 37, 39 and 41-46 were amended.

On May 13, 2009, responsive to the final Official Action dated November 13, 2008, Appellants filed an Amendment and Response in which claims 29-37, 39 and 41, 43-45 were amended. Appellants filed the Amendment and Response with a Request for Continued Examination.

On February 2, 2010, responsive to the final Official Action dated August 6, 2009, Appellants filed an Amendment and Response in which claims 29 and 35 were amended.

On November 24, 2010, responsive to the final Official Action dated March 24, 2010, Appellants filed a Response to Final Official Action in which no claims were cancelled or amended. A Request for Continued Examination was filed with the Response.

No further amendments were made to the claims.

As such, Appellants submit that claims 29-37, 39 and 41-46 are the currently pending claims on appeal as evidenced in the Claims Appendix submitted herewith.

6. Summary of Claimed Subject Matter

Independent claim 29 is directed a method for determining one or more kinetic parameters of binding between a first binding member and a second binding member comprising: simultaneously adsorbing the first binding member to a surface at a plurality of microspots, the adsorbing comprising activating the surface of at least one microspot by presenting thereto a chemical activating substance, the activating comprising forming a first channel around a region containing the at least one microspot, introducing a solution containing the activating substance into the channel, and removing excess activating solution from the channel, adsorbing the first binding member to the at least one microspot, and deactivating the at least one microspot; simultaneously presenting the second binding member at a plurality of concentrations to the first binding member at the plurality of microspots, there being a plurality of combinations of first binding member surface density and second binding member concentrations among the plurality of microspots; simultaneously obtaining one or more kinetic parameters indicative of a binding reaction between the first and second binding members at each of the plurality of microspots to produce a kinetic analysis of the binding, the binding being detected by a biosensor detection method; simultaneously obtaining reference data from a plurality of interspots, each of the interspots located at a surface between at least two or more the microspots; and processing the binding kinetic parameters and the reference data to obtain one or more kinetic parameters characteristic of the binding between the first and second binding members, wherein the plurality of bindings carried out does not require a regeneration step.

Support for independent claim 29 can be found throughout the specification and claims as originally filed. For example, please *see* the as-filed specification at: page 2, line 28 to page 3, line 2; page 4, line 14 to page 5, line 24; page 6, line 8 to 23; and page 11, line 25 to page 28, line 3 (e.g., page 11, line 25 to page 12, line 23; page 17, line 3 to page 21, line 3; page 21, line 8 to page 24, line 10; and page 25, line 8 to page 28, line 3).

Independent claim 37 is directed to a method for localizing a molecular species at each of two or more microspots on a surface, comprising: activating a microspot surface by: forming a first channel around the region containing the microspot; introducing a solution containing an activating substance into the channel; and removing excess activating solution from the channel; simultaneously adsorbing a molecular species to each of the two or more microspots, the adsorbing comprising forming at least two further channels, each being perpendicular to the first channel; simultaneously introducing a solution containing the molecular species into the channel; and optionally deactivating the microspot, wherein the molecular species localized on the two or more microspots may be the same in each of the microspots or different in each of the microspots, and wherein the molecular species may be adsorbed at identical or different surface densities to each of the microspots.

Support for independent claim 37 can be found throughout the specification and claims as originally filed. For example, please *see* the as-filed specification at: page 4, line 1 to page 5, line 24; page 6, line 24 to 30; and page 11, line 25 to page 28, line 3.

7. Grounds of Objection/Rejection to be Reviewed on Appeal

A. Objection to claims 29 and 37

Whether the term "member" should be "members" in claim 29, lines 3 and 14 and claim 37, lines 8 and 12.

B. Rejection of claims 29-31, 33, 35-37, 41, 42 and 46 under 35 USC § 103(a)

Whether claims 29-31, 33, 35-37, 41, 42 and 46 are unpatentable over Winkler et al. (US Patent No. 5,384,261), in view of Ivarsson (US Patent No. 6,493,097) and further in view of Shah (US Patent No. 6,916,621).

C. Rejection of claims 32, 44 and 45 under 35 USC § 103(a)

Whether claims 32, 44 and 45 are unpatentable over Winkler et al. (US Patent No. 5,384,261), in view of Ivarsson (US Patent No. 6,493,097), further in view of Shah (US Patent No. 6,916,621), as applied to claim 29 above, and further in view of Natesan et al. (US Patent Application Publication No. 2002/0048792).

D. Rejection of claims 34 and 49 under 35 USC § 103(a)

Whether claims 34 and 49 are unpatentable over Winkler et al. (US Patent No. 5,384,261), in view of Ivarsson (US Patent No. 6,493,097), further in view of Shah (US Patent No. 6,916,621), as applied to claim 29 and 37 above, and further in view of Siddigi et al. (US Patent No. 5,541,113).

8. Argument

A. Objection to claims 29 and 37

The Examiner asserts that the term "member" should be "members" in claim 29, lines 3 and 14 and claim 37, lines 8 and 12 because, allegedly, there needs to be more than one member for there to be simultaneous adsorbing.

In view of the following, this objection is respectfully traversed.

As set forth in Appellants Amendment and Response dated September 24, 2010, Appellants respectfully submit that the term "simultaneously" may refer to, for example, adsorbing the first binding member at the plurality of microspots, all at the same time, i.e., simultaneously. This would clearly not require more than one binding member to occur simultaneously, as the simultaneous adsorption refers to the adsorption of a single species of binding member at a plurality of microspots.

Thus, Appellants submit the Examiner's interpretation of the claimed subject matter is flawed. In this regard, Appellants submit that the term "simultaneously" in the portions of claim 29 and 37 referred to in the objection does not necessarily refer to adsorbing more than one first binding member. Furthermore, at page 2 of the Official Action dated January 6, 2011, the Examiner asserts that

> Applicant has argued that "simultaneous" in the claims can encompass the first and second binding members simultaneously provided. However, Examiner does not see any support for this interpretation in the specification.

However, it appears that the Examiner has missed Appellants remarks in both the Response to final Official Action submitted on September 24, 2010 and the Amendment and response submitted on February 12, 2010, wherein Appellants explain that simultaneous adsorption of the first binding member at a plurality of microspots occurs, as claimed.

Support for this assertion can be found in the as-filed specification, for example, at page 4, lines 18-21, which provides that:

> ...***a single probe species is adsorbed to microspots on a surface*** such as an SPR surface under a plurality of conditions, for example at different concentrations or pH, in order to obtain different probe densities.

Further support can be found in the as-filed specification, for example, at page 17, lines 7 to 11, which provides that:

> ...***m probe regions 82 are simultaneously activated. 6 probe regions 82a to 82f are shown in Fig. 4a.....The m probe regions 82 are activated and the probe is adsorbed onto the probe regions 82.*** (Emphasis Added).

In view of the foregoing, Appellants submit that the term "member" does not need to be replaced by the term "members." Thus, reconsideration and withdrawal of this objection is respectfully requested.

B. Rejection of claims 29-31, 33, 35-37, 41, 42 and 46 under 35 USC § 103(a)

The Examiner asserts that claims 29-31, 33, 35-37, 41, 42 and 46 are unpatentable over Winkler et al., in view of Ivarsson and further in view of Shah because, allegedly, it would have been obvious to combine the teachings of cited references to obtain certain features of the presently claimed subject matter.

In view of the following, this rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the Examiner must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc.,* 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, 550 U.S. 398 at 417.) Second, the proposed modification of the prior art must

have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Appellants respectfully submit that a *prima facie* case of obviousness has not been established because, whether taken alone or together, the cited references do not teach or suggest every element of the pending claims. In addition, Appellants submit that there would not have been a reasonable expectation of success in combining the references to achieve the presently pending subject matter.

A. ALL ELEMENTS ARE NOT TAUGHT OR SUGGESTED BY THE COMBINATION OF REFERENCES

The presently claimed subject matter is non-obvious because, whether taken alone or together, none of the cited references teach or suggest every element of the presently claimed subject matter.

Claim 29 is directed to a method for determining one or more kinetic parameters of binding between a first binding member and a second binding member comprising: simultaneously adsorbing the first binding member to a surface at a plurality of microspots, the adsorbing comprising activating the surface of at least one microspot by presenting thereto a chemical activating substance, the activating comprising forming a first channel around a region containing the at least one microspot, introducing a solution

containing the activating substance into the channel, and removing excess activating solution from the channel, adsorbing the first binding member to the at least one microspot, and deactivating the at least one microspot; simultaneously presenting the second binding member at a plurality of concentrations to the first binding member at the plurality of microspots, there being a plurality of combinations of first binding member surface density and second binding member concentration among the plurality of microspots; simultaneously obtaining one or more kinetic parameters indicative of a binding reaction between the first and second binding members at each of the plurality of microspots to produce a kinetic analysis of the binding, the binding being detected by a biosensor detection method; simultaneously obtaining reference data from a plurality of interspots, each of the interspots located at a surface between at least two or more the microspots; and processing the binding kinetic parameters and the reference data to obtain one or more kinetic parameters characteristic of the binding between the first and second binding members, wherein the plurality of bindings carried out does not require a regeneration step. Claims 30, 31, 33, 36, 36 and 41-43 depend, either directly or indirectly, from claim 29.

Claim 37 is directed to a method for localizing a molecular species at each of two or more microspots on a surface, comprising: activating a microspot surface by: forming a first channel around the region containing the microspot; introducing a solution containing an activating substance into the channel; and removing excess activating solution from the channel; simultaneously adsorbing a molecular species to each of the two or more

microspots, the adsorbing comprising forming at least two further channels, each being perpendicular to the first channel; simultaneously introducing a solution containing the molecular species into the channel; and optionally deactivating the microspot, wherein the molecular species localized on the two or more microspots may be the same in each of the microspots or different in each of the microspots, and wherein the molecular species may be adsorbed at identical or different surface densities to each of the microspots. Claim 46 depends indirectly from claim 37.

Winkler et al. is directed to method and device for forming large arrays of polymers on a substrate. The polymers are prepared by flowing of monomers over the substrate in a serial fashion, i.e., a first monomer is provided, then a second monomer, etc. Ivarsson is directed to a method of examining thin layer structures on a surface for differences in respect of optical thickness. Shah is directed to computer systems, computer program products and methods utilized in silico array-based methods for determining the relative amount of biological molecules in two or more samples. *See* each of Winkler et al., Ivarsson and Shah at the respective abstracts.

However, unlike the presently claimed subject matter, Appellants respectfully submit that:

(I) whether taken alone or in combination, none of the cited references teach or suggest "simultaneously presenting the second binding member at a plurality of concentrations to the first binding member the plurality of microspots, there ***being a plurality of combinations of first binding member surface density and second binding***

member concentrations among the plurality of microspots," or adsorption the molecular species at "different surface densities to each of the microspots," as recited in claims 29 and 37;

(II). whether taken alone or in combination, none of the cited references teach or suggest a method that which would not require a regeneration step in order to perform the an analysis of different surface densities of a single first binding member species in the presence of a plurality of concentrations of second binding member, as claimed;

(III) whether taken alone or in combination, none of the cited references teach or suggest "simultaneously adsorbing the first binding member to a surface at a plurality of microspots," or "simultaneously adsorbing a molecular species to each of the two or more microspots…[by] simultaneously introducing a solution containing the molecular species into the channel," as recited in claims 29 and 37; and

(IV) "simultaneous analysis" is not taught or suggested by the cited references since the general disclosure of a "simultaneous analysis" does not necessarily describe the determination of a kinetic parameter, e.g., Kd and Ka.

Appellants submit that nowhere, in any of the cited references, is there a teaching, or even a remote suggestion, for "simultaneously presenting the second binding member at a plurality of concentrations to the first binding member the plurality of microspots, there being a plurality of combinations of first binding member surface density and second binding member concentrations among the plurality of microspots," or adsorption the molecular species at "different surface densities to each of the microspots," as recited in

claims 29 and 37. In this regard, ***the cited references do not teach or suggest a first binding member or single molecular species at a plurality of surface densities***. Appellants note that the first binding member being present simultaneously at plurality of surface densities in combination with the presentation of the second binding member in a plurality of concentrations, is tantamount to the unexpectedly superior speed and efficiency realized when performing the claimed methods. This combination of features makes it possible to obtain data for multiple combinations of different surface densities of a single species of first binding member for multiple concentrations of a single second binding member, without the need for regeneration.

Conventionally, to determine a kinetic parameter of, e.g., association and dissociation rate constants (k_a and k_d, respectively), for the interaction between two interacting molecules (i.e., a first and second binding members in claim 29), one of the molecules is immobilized to a sensor surface and the other molecule, often referred to as the analyte, is provided in solution at several different known concentrations.

The conventional method at the time of filing of the present application was to bring different analyte concentrations into contact with ***the same first binding surface***. Such contact of different sample concentrations with the ***same*** first binding surface provides inherent measurement reproducibility resulting from using the same first binding member. Naturally, such reproducibility is of critical importance in determination of a kinetic parameter, which is a very sensitive procedure in contrast to mere detection of a binding reaction.

Conducting such contacting with ***the same first binding surface*** dictates ***serial*** analysis, an experiment performed along a linear time line each time section is devoted to a particular sample concentration. This view was also made of record in Prof. Gideon Schreiber's declaration, stating that the paradigm at the time was that kinetic analysis required serial operation and performance of a regeneration step. Please *see* the Schreiber declaration attached hereto.

For one of ordinary skill to even consider conducting parallel processing of a plurality of analyte concentrations, he/she would first have to decide to move away from the conventional method, which dictates flowing different sample concentrations to contact ***one and the same first binding surface***. Appellants submit that this dictates ***serial*** analysis of the same first binding member and thus requires regeneration.

Turning to Winkler et al., Appellants note that Winkler et al. state that:

> [t]he present invention relates ***to the field of polymer synthesis***. More specifically, in one embodiment the invention provides an improved method and ***system for synthesizing arrays of diverse polymer sequences***. (Emphasis added). *See* Winkler et al. at column 1, lines 7-10.

The inventors of Winkler et al., by their own admission indicate that "...[t]he process is repeated ... By virtue of the process, ***a number of polymers having diverse monomer sequences*** such as peptides or oligonucleotides are formed on the substrate at known locations." (Emphasis added). *See* Winkler et al. at column 2, lines 17-20. Winkler et al. require the serial addition of several monomer sequences to obtain a

polymer, which is not equivalent to the adhesion of a single first binding member at a plurality of microspots.

Appellants submit that the binding reactions in Winkler et al. merely assess if one or more of the "diverse peptides" binds a receptor. For example, according to Winkler et al. at column 6, lines 15-20 e.g., "in preferred embodiments the invention provides for screening of peptides ***to determine which if any of a diverse set of peptides has strong binding affinity with a receptor*** and, in most preferred embodiments to determine the relative ***binding affinity of various peptides with a receptor of interest*** such as an antibody." Therefore, Appellants note that, for example, Winkler et al. tests whether any of proteins A, B, ... D bind with a receptor, R. Appellants respectfully submit that this may be referred to as "many proteins to one receptor."

The technology in Winkler et al. merely includes binding reactions to test whether a receptor binds (or relatively binds) any of the ***diverse peptide sequences*** being synthesized. As discussed herein below, Winkler et al.'s description of delivery of molecules by gravity assisted free-fall and/or pipettor placement, and/or conventional channeling techniques to pull molecules along the channel blocks, would not lead one of ordinary skill in the art to abort the conventional protocol, which dictates repeated serial reactions on the same binding surface.

Appellants submit that this is completely different from the presently claimed subject matter which recites the determination of ***a kinetic parameter*** (e.g., K_d and K_a) of ***a protein pair*** (i.e., first and second binding members combinations such as those in

claim 29) by parallel analysis of different analyte concentrations (e.g., the second binding member in claim 29) at a plurality of microspots.

Contrary to the Examiner's assertion, neither Ivarrson nor Shah remedy the deficiencies of Winkler et al. Neither Ivarrson nor Shah teach or suggest any of items (I)-(IV) above.

Nonetheless, the Examiner asserts that:

> Using the Winkler device as discussed above does not necessitate a regeneration step in order to provide the different concentrations of analyte since they are provided through the different channels and detected simultaneously, as this is understood to be the case for the analyte as it is for the process of immobilizing the first binding reagent. The skilled artisan would have had reasonable expectation of success in performing kinetic analysis (suggested by Ivarrson) with different concentrations of analyte in the different channels because it is predictable that the same binding detection can be made in each channel over a period of time to obtain kinetic data. *See* the Official Action dated January 6, 2011 at page 8, third paragraph.

Appellants note that the Examiners assertion is flawed because, in fact, ***it would be necessary to perform a regeneration step in order to obtain binding data for different surface densities of a single species of a first binding member.*** In this regard, the Examiner completely ignores the claimed feature simultaneously presenting and/or obtaining data for "***a plurality of combinations of first binding member surface density and second binding member concentrations.***"

Additionally, Appellants submit that the Examiners assertion is flawed because it admits that the proposed combination would require "the same binding detection can be made in each channel over a period of time to obtain kinetic data," which is contrary to

the claimed method that does not require serial processing. In addition, it would also suggest that it would not have been obvious to utilize both a plurality of surface densities for a single species of binding member and a plurality of concentrations of second binding member ***at the same time***.

Appellants submit that none of the references cited directs one of ordinary skill in the art to combine molecules as claimed, i.e., "***a plurality of combinations of first binding member surface density and second binding member concentrations***." Instead, Appellants submit that the cited art suggests repeated experiments on the same first binding member surface.

In addition, the Examiner next asserts that:

> In other words, it is predictable by the skilled artisan that simultaneously detecting binding kinetics by simultaneously providing different concentration of a reagent in each channel, with the same binding agents in each channel, is a functional equivalent to detecting binding kinetics by increasing concentration of a reagent in the same channel over time. It is predictable that these two methods are functional equivalences because in each method, there are detections between one bound reagent, and another reagent, with different concentrations (from which kinetic data can be obtained, as is well understood in the art, and as disclosed by Ivarrson).*See* the Official Action dated January 6, 2011 at page 8, third paragraph.

However, Appellants submit that the proper analysis for obvoiousness under 35 USC § 103(a) does not include a determination of whether serial processing is functionally equivalent to simultaneous processes, i.e., adhesion, activation and analysis; but, whether the cited references teach or suggest the claimed subject matter. Thus, while Appellants welcome the Examiner's comments suggesting that two different processes may be

functionally equivalent, Appellants respectfully note that these comments are irrelevant since there is no known teaching, suggestion or reasonable expectation of success in achieving the claimed method. In this regard, the only suggestion or motivation that the Examiner offers is that which has been derived from the present application and claims.

In addition, Appellants note that the Examiner has been provided with evidence in the form of literature references, Rich et al., *Higher-throughput, label-free, real-time molecular interaction analysis*, Analytical Biochemistry, 361 (2007) 1–6, a 2006 (discussed in § II(B) below and submitted herewith), which expressly rebuts the assertion that the state of the art at the time of filing of the present application would have included deviation from the "conventional" method discussed herein above.

Appellants submit that Winkler et al.'s "many proteins to one receptor" technique, described above, does not teach or suggest the claimed features even if the receptor is provided in different concentrations, e.g., Winkler et al. do not teach or suggest the combination of a more than one surface density of a single species of first binding member and a second binding member at varying concentrations, e.g.: A_xB_y (AB_1), (AB_2), (AB_1), (A_1B_2), (A_1B_3), (A_2B_1), (A_2B_2), (A_2B_3) etc., where A is a specific immobilized first binding member, x refers to a single surface density for a species of the first binding member, B is a second binding member, and y refers to a single concentration of second binding member solution.

To the contrary, the technique described by Winkler et al. forms a diverse array of peptides with maximal number of different (diverse) peptides. Winkler et al. do not teach

or suggest providing "a method for determining one or more kinetic parameters of binding between a first binding member and a second binding member .... there being a plurality of combinations of first binding member surface density and second binding member concentrations among the plurality of microspots…to obtain one or more kinetic parameters characteristic of the binding between the first and second binding members, as recited, in claim 29.

With regard to the simultaneous analysis, the Examiner states that

> Thus the skilled artisan is suggested to utilize known photodetection techniques, such as that disclosed by Ivarrson that provides the ***benefit of simultaneous analysis, such as kinetic analysis of different sensor zones***. *See* the Official Action at page 8, 3rd paragraph.

In fact, Ivarrson merely describes photo-detection techniques that may occur simultaneously. The Examiner acknowledges that Ivarrson does not describe determination of a kinetic parameter, i.e., "…simultaneous analysis, such as kinetic analysis." Appellants submit that the single phrase in Ivarrson, according to which "mass distribution kinetic data for, e.g. sample binding/desorption" (*see* Ivarrson at column 23, line 63), is too general and unclear to be taken as meaning a "plurality of combinations of first binding member surface density and second binding member concentrations among the plurality of microspots," rather than the conventional recurrent use of the same first binding member. Thus, Appellants submit that the cited art does not rise to a determination of a kinetic parameter obtained from the combinations, as claimed by the pending claims.

Appellants submit that the process of binding the ***first*** binding member descried by Winkler et al. cannot be considered "simultaneously adsorbing…," as claimed. In this regard, Appellants submit that Winkler et al. describe a ***serial multi-step process to synthesize the first binding member***, i.e., a *de-novo in-situ* gradual coupling of building blocks to create a first binding member on the surface. Appellants note that this process includes building of one monomer (amino acid) on top of the former until the whole polymer (peptide) is gained. Additionally, it includes many chemical steps, washing steps, rotation of channels or opening valves. However, Appellants submit that even if the monomers are transported to more than one spot, there is no disclosure of ***simultaneous adsorbing of the first binding member***.

Moreover, as the technique described by Winkler et al. forms ***a diverse array of peptides***, there is no suggestion of synthesizing the first binding member in more than one spot, let alone "adsorbing" the first binding member in plurality of microspots. Thus, "simultaneously adsorbing the first binding member to a surface at a ***plurality*** of microspots" is not disclosed by Winkler et al. Further, the remaining references do not remedy the deficiencies of Winkler et al. Therefore, the cited references do not render the presently claimed subject matter obvious.

Additionally, Appellants submit that there is no disclosure in any of the references cited by the Examiner that an experiment to determine a kinetic parameter, which by convention is conducted on the same first binding surface, could ever be performed on a plurality of different binding surfaces. Accordingly, Appellants submit that there is no

teaching or suggestion, in any of the cited references to abort the inherent reproducibility of serial analysis for parallel analysis with the Winkler et al. device.

In view of the foregoing, Appellants respectfully submit that nothing in Winkler et al., Ivarsson and Shah, whether taken alone or together, teach or suggest every element of the presently claimed subject matter. Therefore, the claimed subject matter is not obvious.

B. NO REASONABLE EXPECTATION OF SUCCESS

The Examiner states that:

> [g]iven the improvements of Ivarrson, the skilled artisan would have had reasonable expectation of success in providing such improvements to the Winkler et al. invention to allow for simultaneous analysis in the different zones. See the Official Action at the bottom page 9.

As previously stated, the presently claimed subject matter is directed to more than simultaneous analysis in the different zones. For example, the pending claims are directed to analyzing data obtained from a plurality of combinations of first binding member surface density and second binding member concentrations among the plurality of microspots.

In contrast, Appellants submit that the cited art merely suggests the conventional recurrent use of the same first binding member. Kinetic parameter determination obtained from the arrived combinations is not taught or suggested by any of the cited references.

Nonetheless, the Examiner appears to propose a device combination to conduct parallel analysis and processing of a plurality of analyte concentrations to produce kinetic

analysis instead of the serial techniques in the state of the art. However, Appellants submit that the Examiner's assertion that parallel analyte processing for determine kinetic parameters was known/readily available is without merit and should be withdrawn. In this regard, the state of the art prior to the filing of the application can be appropriately derived from Rebecca L. Rich, David G. Myszka, *Higher-throughput, label-free, real-time molecular interaction analysis*, Analytical Biochemistry, 361 (2007) 1–6, a literature publication submitted in the captioned application on February 12, 2010. Appellants submit that the Rich publication reviews the development of kinetic analysis starting from the 1990s until about 2006. The only two *parallel analyte* processing systems for determination kinetic parameter are that of Biacore A100 and the ProteOn XPR36, which is owned by the assignee of the present subject matter. Both devices were made available to the public around 2005.

According to the Rich publication at page 4, right column:

> The ***Proteon system [i.e, the technology claimed in the present application] also introduces a novel concept in kinetic analysis*** referred to as "one-shot" kinetics. ***With this approach one can simultaneously test six different concentrations of analyte over the different target surfaces,*** thereby generating a full analyte concentration series with one injection [25,26]. This reduces analysis time significantly and eliminates the need for surface regeneration.

In addition, in a separate 2006 publication, i.e., Bravman T, Bronner V., Lavie K., Notcovich A, A. Papalia G , Myszka DG, *Exploring "one-shot" kinetics and small molecule analysis using the ProteOn XPR36 array biosensor*, Analytical Biochemistry, 358 (2006) 281-288 (herein after the Bravman publication), the following was stated:

> The use of crisscrossing flow paths provides for a number of interesting experimental applications. One of the first applications we wanted to explore was the ability to ***collect kinetic data for six different concentrations of analyte at the same time. Historically, response data for different analyte samples have been collected sequentially. Parallel collection of different analyte concentrations could improve sample throughput and also render obsolete the need to regenerate the target sensor surface***." (Emphasis Added). *See* the Bravman publication at page 282, left column, second paragraph.

This is further supported by US Published Patent Application No. 2005/0014179 (the '179 application, a copy of which is submitted herewith), assigned to Biocore and previously cited by the Examiner. Paragraph [0006] of the '179 application recognizes that:

> ***Conventionally, to determine, for example, association and dissociation rate constants (k_a and k_d, respectively) for the interaction between two interacting molecules, one of the molecules, often referred to as the ligand, is immobilized to a sensor surface and the other molecule, often referred to as the analyte, is provided in solution at several different known concentrations.*** Each concentration, or sample, of the analyte is then contacted with the sensor surface, either in a laminar flow past the sensor surface, or in a cuvette or the like, to permit association of the analyte to the sensor surface. After a sample has been brought to contact the sensor surface, the surface is contacted with a solution free from analyte, usually buffer, to permit dissociation of the analyte from the immobilized ligand. During these association and dissociation phases, the amount of binding of analyte to the surface is continuously detected and the binding data is collected. ***Before contacting the sensor surface with sample of a new analyte concentration, the ligand surface is restored or "regenerated" by treating the surface with a regeneration solution capable of removing any bound analyte while not destroying the ligand. In that way, all the different samples will contact essentially one and the same ligand surface as far as ligand density is concerned.*** The association and dissociation rate constants can then be obtained from the collected binding data by fitting the data to mathematical descriptions of interaction models in the form of differential equations. Usually, the binding data for all the samples are used in the same fit, a procedure

referred to as global fitting. From the determined association and dissociation rate constants k_A and k_d, the equilibrium constant, K_D, and the affinity constant K_A (K_A =1/ K_D) of the interaction can in turn be calculated. (Emphasis Added).

Paragraphs 15 and 16 of the '179 publication goes on to indicate that:

[f]rom the prior art it may therefore be concluded that for determining kinetic rates for molecular interactions using systems based on biosensors and affinity analysis, ***it is necessary to regenerate the immobilized ligand prior to contacting the sensor surface with a different concentration of analyte to thereby present essentially one and the same ligand surface to each analyte concentration,*** unless (i) a continuous gradient of the analyte is used, or (ii) initial binding rates are determined in systems free from mass transport limitations.

It is an object of the present invention to provide a sensor-based method for determining chemical interaction parameters, including kinetic rate constants, by stepwise titration, which method obviates regeneration procedures while permitting measurements under mass transport limitation. (Emphasis Added).

As already stated, for one of ordinary skilled to even consider conducting parallel processing of plurality of analyte concentrations, she would first have to decide to move away from the conventional method, which dictates flowing different sample concentrations to contact ***one and the same first binding surface.***

Therefore, Appellants respectfully submits that at the filing date there was "no reasonable expectation of success" to conduct parallel analysis and processing of a plurality of analyte concentrations over a plurality of binding surfaces to produce kinetic analysis instead of the serial techniques in the state of the art. On the other hand, there was a reasonable expectation that a regeneration step would be required.

Appellants submit that there is no "reasonable expectation of success" because of the technological limitations in the device of Winkler et al. Figures **4A-4B** of Winkler et al. and the accompanying text reveal that the Winkler et al. device is inappropriate for the use in determining a kinetic parameter, for at least the following reasons: (1) the process of binding the **first** binding member is actually a process of artificial synthesis of a first binding member; (2) the repeated synthesis cycles are likely to insert additional unpredictable variables; (3) The gravity assisted free-fall delivery technique described by Winkler et al. is vulnerable to inaccuracies and is incompatible with determination of kinetic parameters; (4) the lack of uniform surface densities shown in Winkler et al. is incompatible with the aim of determination of a kinetic parameter; (5) the Winkler et al. device is a synthesis platform; and (6) the second binding member in Winkler et al., i.e, the receptor molecule, is merely used for evaluation of relative binding affinity.

With regard to item (1), the process of binding the **first** binding member is actually a process of artificial synthesis of a first binding member. Winkler et al describe a ***serial*** multi-step process that contains building of one monomer (amino acid) on top of the former one until the whole polymer (peptide) is gained. It includes many chemical steps, washing steps, de-protecting steps, rotation of channels or opening valves.

This technological limitation of *de-novo in-situ* synthesis the first binding member (instead of adsorbing the first binding member in claim 29) dictates that Winkler cannot verify that all proteins synthesized are uniformly created (in terms of sequence and/or spatial distribution on the spot).

Moreover, it is further known that amino-monomers coupling inefficiency exists in artificial synthesis of proteins. This inefficiency increases in correlation with the length of the synthesized proteins.

One of ordinary skill in the art would not reasonably expect success by employing the Winkler et al. device, which would bring about any number of unpredictable new variable(s), e.g., coupling inefficiency, distribution of variety of protein sequences, etc., to the determination of a kinetic parameter. As this is already highly sensitive procedure, one of ordinary skills in the art would not resort to a peptide synthesis platform to conduct determination of kinetic parameters.

With regard to (2), the repeated synthesis cycles are likely to insert additional unpredictable variables into the already sensitive procedure of determination of the kinetic parameter.

Regarding (3), figure **4B** in Winkler shows a pipettor **417** which is slidably mounted on arm **419** to deliver selected molecules. In figure **4B**, delivery seems to be actuated in a gravity assisted free-fall manner, from reservoir(s) **421** to flow inlets **411**. The gravity assisted free-fall delivery technique described by Winkler et al. is vulnerable to inaccuracies and is incompatible with determination of kinetic parameters. Similarly, pipettor placement will also result with the same inaccuracies.

With regard to (4), the intensity mapping showed in figures **9-10** of Winkler et al. is evidence of increased signal which can be explained by correlation of signal intensity to proximity to the vacuum source to the signal location. Such lack of uniform surface

densities, as can be seen in example B and figure **10**, is incompatible with the aim of determination of a kinetic parameter.

Regarding item (5), the channel blocks (**407**) which transport molecules along the substrate defined by Winkler et al. seems to be of much greater dimensions than the microchannels which are utilized by the presently claimed subject matter. Appellants submit that this is inappropriate for the transport of minute solution quantities required for the determination of a kinetic parameter. The Winkler et al. device is a synthesis platform, as previous described, and as such it does not address the required channeling.

With regard to (6), the second binding member in Winkler et al., i.e, the receptor molecule, is merely used for ***evaluation of relative binding affinity***. *See,* e.g., Winkler et al. at column 6 lines, 18-31 and example B. Not only are kinetics not mentioned by Winkler et al., but the proposed array device produces signals which are used for comparative evaluation and not as a mechanism for providing measurements accurate enough for any numerical value.

As stated, the array described by Winkler et al. is designed to screen peptides bind more strongly to a specific antibody by comparing the intensity of a fluorescent signal. Even this works rather roughly due to non-uniform surface densities, as can be seen in example B and figure **10**.

Thus, Appellants submit that the option of using several "receptor" concentrations (col. 11 lines 32-35) cannot be for the purpose of kinetic measurement or for any numerical analysis. In this regard, it is just another option for comparative screening, for

which no "reasonable expectation of success" can be attributed to if applied for determination of kinetic parameters.

In view of the foregoing, Appellants submit that a skilled artisan would not have had a reasonable expectation of success in obtaining the claimed methods, which do not require a regeneration step. Thus, presently claimed subject matter is not obvious

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination, none of the cited references render the presently pending claims obvious within the meaning of 35 USC § 103(a). Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

C. Rejection of claims 32, 44 and 45 under 35 USC § 103(a)

The Examiner asserts that claims 32, 44 and 45 are unpatentable over Winkler et al., in view of Ivarsson, further in view of Shah, as applied to claim 29 above, and further in view of Natesan et al. because, allegedly, it would have been obvious to combine the teachings of cited references to obtain certain features of the presently claimed subject matter.

In view of the following, this rejection is respectfully traversed.

The relevant authority regarding obviousness under 35 USC § 103 is set forth above. For a detailed discussion of the authority on obviousness please *see* § II above.

Claims 32, 44 and 45 depend, either directly or indirectly, from claim 29. The presently claimed subject matter, Winkler et al., Ivarsson and Shah are discussed in detail above in § II.

As discussed:

(I) whether taken alone or in combination, none of Winkler et al., Ivarsson and Shah teach or suggest "simultaneously presenting the second binding member at a plurality of concentrations to the first binding member the plurality of microspots, there ***being a plurality of combinations of first binding member surface density and second binding member concentrations among the plurality of microspots***," or adsorption the molecular species at "different surface densities to each of the microspots," as recited in claims 29 and 37;

(II) whether taken alone or in combination, none of Winkler et al., Ivarsson and Shah teach or suggest a method that which would not require a regeneration step in order to perform the an analysis of different surface densities of a single first binding member species in the presence of a plurality of concentrations of second binding member, as claimed;

(III) whether taken alone or in combination, none of Winkler et al., Ivarsson and Shah teach or suggest "simultaneously adsorbing the first binding member to a surface at a plurality of microspots," or "simultaneously adsorbing a molecular species to each of the two or more microspots…[by] simultaneously introducing a solution containing the molecular species into the channel," as recited in claims 29 and 37; and (IV) "simultaneous

analysis" is not taught or suggested by the cited references since the general disclosure of a "simultaneous analysis" does not necessarily describe the determination of a kinetic parameter, e.g., Kd and Ka. Furthermore, based on the state of art at the time of filing of the present application, a skilled artisan would not have had a reasonable expectation of success in obtaining the presently claimed subject matter.

Natesan et al. do not remedy the deficiencies of Winkler et al., Ivarrson and Shah. Natesan et al. is directed to a method for regulated production of a desired protein in cells, which comprises providing cells containing recombinant nucleic acids encoding at least one fusion protein which binds to a selected ligand, wherein the fusion protein comprises a ligand binding domain and a DNA binding domain.

However, like Winkler et al. Ivarrson and Shah, Natesan et al. do not teach or suggest the items mentioned in items (I)-(IV), above. Accordingly, the combination of references does not render the presently claimed subject matter obvious.

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination, none of the cited references render the presently pending claims obvious within the meaning of 35 USC § 103(a). Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

D. Rejection of claims 34 and 49 under 35 USC § 103(a)

The Examiner asserts that claims 34 and 49 are unpatentable over Winkler et al., in view of Ivarsson, further in view of Shah, as applied to claim 29 and 37, and further in view of Siddigi et al. because, allegedly, it would have been obvious to combine the teachings of cited references to obtain certain features of the presently claimed subject matter.

In view of the following, this rejection is respectfully traversed.

The relevant authority regarding obviousness under 35 USC § 103 is set forth above. For a detailed discussion of the authority on obviousness please *see* § II above. Claims 32, 44 and 45 depend, either directly or indirectly, from claim 29. The presently claimed subject matter, Winkler et al., Ivarsson and Shah are discussed in detail above in § II.

As discussed:

(I) whether taken alone or in combination, none of Winkler et al., Ivarsson and Shah teach or suggest "simultaneously presenting the second binding member at a plurality of concentrations to the first binding member the plurality of microspots, there ***being a plurality of combinations of first binding member surface density and second binding member concentrations among the plurality of microspots***," or adsorption the molecular species at "different surface densities to each of the microspots," as recited in claims 29 and 37;

(II) whether taken alone or in combination, none of Winkler et al., Ivarsson and Shah teach or suggest a method that which would not require a regeneration step in order to perform the an analysis of different surface densities of a single first binding member species in the presence of a plurality of concentrations of second binding member, as claimed;

(III) whether taken alone or in combination, none of Winkler et al., Ivarsson and Shah teach or suggest "simultaneously adsorbing the first binding member to a surface at a plurality of microspots," or "simultaneously adsorbing a molecular species to each of the two or more microspots…[by] simultaneously introducing a solution containing the molecular species into the channel," as recited in claims 29 and 37; and (IV) "simultaneous analysis" is not taught or suggested by the cited references since the general disclosure of a "simultaneous analysis" does not necessarily describe the determination of a kinetic parameter, e.g., Kd and Ka. Furthermore, based on the state of art at the time of filing of the present application, a skilled artisan would not have had a reasonable expectation of success in obtaining the presently claimed subject matter.

Siddigi et al. do not remedy the deficiencies of Winkler et al., Ivarrson and Shah. Siddigi et al. is directed to a method for detecting analyte in an aqueous solution at a physiological pH, by reductive or oxidative electrochemical luminescence methodologies, which method proceeds by labeling the analyte with a transition metal complex, followed by inducing the transition metal label to luminescence by application of a suitable electrical potential to a solution containing the label and the analyte.

However, like Winkler et al. Ivarrson and Shah, Siddigi et al. do not teach or suggest the items mentioned in items (I)-(IV), above. Accordingly, the combination of references does not render the presently claimed subject matter obvious.

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination, none of the cited references render the presently pending claims obvious within the meaning of 35 USC § 103(a). Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Appellants submit that the application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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9. Claims Appendix

Listing of Claims:

1-28 (Cancelled)

29. (Previously Presented) A method for determining one or more kinetic parameters of binding between a first binding member and a second binding member comprising:

simultaneously adsorbing the first binding member to a surface at a plurality of microspots, the adsorbing comprising

activating the surface of at least one microspot by presenting thereto a chemical activating substance, the activating comprising

forming a first channel around a region containing the at least one microspot,

introducing a solution containing the activating substance into the channel, and

removing excess activating solution from the channel,

adsorbing the first binding member to the at least one microspot, and

deactivating the at least one microspot;

simultaneously presenting the second binding member at a plurality of concentrations to the first binding member at the plurality of microspots, there being a

plurality of combinations of first binding member surface density and second binding member concentrations among the plurality of microspots;

simultaneously obtaining one or more kinetic parameters indicative of a binding reaction between the first and second binding members at each of the plurality of microspots to produce a kinetic analysis of the binding, the binding being detected by a biosensor detection method;

simultaneously obtaining reference data from a plurality of interspots, each of the interspots located at a surface between at least two or more the microspots; and

processing the binding kinetic parameters and the reference data to obtain one or more kinetic parameters characteristic of the binding between the first and second binding members,

wherein the plurality of bindings carried out does not require a regeneration step.

30. (Previously Presented) The method according to claim 29, wherein the biosensor detection method is selected from the group consisting of surface plasmon resonance (SPR), critical angle refractometry, total internal fluorescence (TIRF), total internal reflection phosphorescence, total internal reflection light scattering, evanescent wave elipsometry and Brewster angle reflectometry.

31. (Previously Presented) The method according to claim 29, wherein the detection method is SPR and the data indicative of a binding reaction between the first and second binding members at each of the plurality of microspots is an SPR parameter selected from the group consisting of SPR resonance angle, resonance wavelength, reflectance changes and phase changes.

32. (Previously Presented) The method according to claim 29, wherein the one or more kinetic parameters are selected from the group consisting of an association constant K_a, a dissociation constant K_d and an affinity constant.

33. (Previously Presented) The method according to claim 29, wherein the step of adsorption to the microspot involves

forming a channel around a region containing the microspot,

introducing a solution containing the molecular species into the channel, and

removing excess solution from the channel.

34. (Previously Presented) The method according to claim 29, wherein the step of activating the surface of the microspot comprises producing an electric field over the microspot.

35. (Previously Presented) The method according to claim 29, further comprising:

deactivating portions of the surface not included in a microspot;

forming one or more second channels perpendicular to one or more of the first channels; and

for each second channel, introducing into the second channel a second binding member.

36. (Previously Presented) The method according to claim 29 further comprising obtaining reference data from a region of the surface not included in the microspots.

37. (Previously Presented) A method for localizing a molecular species at each of two or more microspots on a surface, comprising:

activating a microspot surface by:

forming a first channel around the region containing the microspot;

introducing a solution containing an activating substance into the channel; and

removing excess activating solution from the channel;

simultaneously adsorbing a molecular species to each of the two or more microspots, the adsorbing comprising

forming at least two further channels, each being perpendicular to the first channel;

simultaneously introducing a solution containing the molecular species into the channel; and

optionally deactivating the microspot,

wherein the molecular species localized on the two or more microspots may be the same in each of the microspots or different in each of the microspots, and

wherein the molecular species may be adsorbed at identical or different surface densities to each of the microspots.

38. (Cancelled)

39. (Previously Presented) The method according to claim 37, wherein the step of activating the microspot comprises producing an electric field over the microspot.

40. (Cancelled)

41. (Previously Presented) The method according to claim 37, wherein at least one of the molecular species is a first binding member and the method further comprises

forming one or more channels in a region containing the microspots;

introducing a second binding member into each of the one or more channels; and

simultaneously obtaining data indicative of a binding reaction between the first and second binding members at each of the two or more microspots by a biosensor detection method.

42. (Previously Presented) A probe array produced by the method of claim 37.

43. (Previously Presented) The method according to claim 30, wherein the detection method is SPR and the data indicative of a binding reaction between the first and second binding members at each of the plurality of microspots is an SPR parameter selected from the group consisting of SPR resonance angle, resonance wavelength, reflectance changes and phase changes.

44. (Previously Presented) The method according to claim 30, wherein the one or more kinetic parameters are selected from the group consisting of an association constant K_a, a dissociation constant K_d and an affinity constant.

45. (Previously Presented) The method according to claim 31, wherein the one or more kinetic parameters are selected from the group consisting of an association constant K_a, a dissociation constant K_d and an affinity constant.

46. (Previously Presented) A probe array produced by the method of claim 41.

10. Evidence Appendix

Following the "Related Proceedings Appendix" please find submitted herewith, copies of:

(1) Declaration of Professor Gideon Schreiber, sixteen (16) pages, submitted on February 12, 2010;

(2) Bravman T, Bronner V, Lavie K, Notcovich A, A. Papalia G , Myszka DG, *Exploring "one-shot" kinetics and small molecule analysis using the ProteOn XPR36 array biosensor*, Analytical Biochemistry, 358 (2006) 281-288, eight (8) pages, submitted on February 12, 2010;

(3) Rich R, Myszka D, *Higher-throughput, label-free, real-time molecular interaction analysis*, Analytical Biochemistry, 361 (2007) 1–6, six (6) pages, submitted on February 12, 2010; and

(4) US Published Patent Application No. 2005/0014179, twenty-seven (27) pages, cited by the Examiner in the Official Action dated November 13, 2008.

11. Related Proceedings Appendix

No information is appended under this section.